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Balancing the economics and ethics of personalised oncology

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18 **Abstract**

19 The cost of personalised medicine in oncology is increasing. The varied and contrasting priorities of
20 the pharmaceutical industry, local and national governments, international medical community, and
21 patients need to be reviewed and balanced. In addition to the economic and political standpoints on
22 this issue, the ethical considerations from physicians' viewpoints need to be considered to optimise
23 cancer patients' care. In this paper we discuss the way research and development of these drugs is
24 carried out and reimbursed, and how this needs to change. We describe frameworks assessing the
25 value of these treatments which been developed. Physicians need to develop their knowledge and
26 understanding of these issues, to best meet their dual responsibilities of advocating for their
27 patients and promoting public health.

28

29 ***The Cost of Cancer***

30 Cancer is expensive. Worldwide, the financial cost to an individual has been shown to be
31 significant. In the UK where healthcare is free at the point of delivery, a Macmillan charity
32 report found the cost of a cancer diagnosis resulted in being ~£570 a month poorerⁱ. A
33 diagnosis of cancer in the US increases the chance of bankruptcy by 250% [1]. In addition to
34 expense to the patient, cancer is expensive at every level of local and national health
35 systems, and increasingly so. The changing face of oncology with the development of
36 personalised medicine and associated meaningful improvements in survival and treatment
37 toxicity [2], has the potential to revolutionise care, but comes at a price. This price relates to
38 not only the drug itself but the care process with a crucial role of molecular characterisation
39 of tumours, which may need to be rebiopsied and/or sequenced at relapse. Even with rapid
40 development, potential benefit is only for a minority; a recent study identified the

proportion of US patients estimated to benefit from genome-targeted therapy in 2006 to be 0.7%, in 2018 this had increased to just 4.9% [3]. However there is the potential for personalised cancer medicine to minimise cost, for example a gene expression assay has recently been shown to predict chemotherapy benefit and identify patients with breast cancer at low risk of recurrence who can be spared chemotherapyⁱⁱ. The concept of ‘value’ is important, and numerous frameworks have been developed to assess the value of new drugs. These can include for example efficacy, toxicity, and quality of life. Value-based pricing describes the pricing of a drug based on assessment of its benefits and risks.

The price of drugs

In 2000 the average cost of one year of a new systemic anti-cancer therapy (SACT) was less than US\$10,000. In 2016 a new medicine for a similar indication could cost in excess of US\$100,000 for same duration of treatment. The US Agency for Health Care Research and Quality reported a total spend of \$88.7 Billion in 2011ⁱⁱⁱ and the European Union reported spending €126 Billion in 2009 [4]. The cost of developing a new drug has been estimated at \$2.6 Billion in 2014^{iv}], representing a remarkable almost three-fold increase in the cost of developing new drugs. However, the price of new cancer drugs has increased *ten-fold* over approximately the same period, with little evidence that improvements in patient outcomes have kept pace. While these costs are not exclusively due to the use of personalised medicine in oncology, as traditional treatment chemotherapy and radiotherapy still play a significant role, they are responsible for the brunt of it. In addition to the cost of the drug itself, there are also the costs of companion diagnostics, development costs, and relevant associated technology.

At the same time as the costs of cancer care are spiralling ever upwards, the growth in total healthcare expenditure in developed countries has continued to outstrip the rate of economic growth, and public sector funding of healthcare is up to 46% of total public expenditure in some countries^v. Against this background, the economics of healthcare provision in oncology is no longer an esoteric question of interest to a niche community of academics. To sustain high quality cancer care it is vital to understand the cost drivers in the current management of cancer and identify where the choices we make for the future of cancer care improve value for money.

So why are these anti-cancer drugs so expensive? One argument to justify this is that these therapies have demonstrated an improvement in quality and extension of life. Viewed in terms of Quality Adjusted Life Years (QALYs), the mean incremental health gain from specialty drugs (personalised therapies defined by the authors as 'large molecule' drugs produced using advanced biotechnology requiring special administration, monitoring and handling) launched between 1999 and 2011 has been valued at 0.25 QALYs compared with 0.08 for traditional drugs [5]. Twenty two of these 58 drugs were for cancer. Another factor is that targeted therapies, almost by definition, are suitable for fewer patients than previous systemic therapies. This therefore means the commercial return on R&D investment must be achieved from fewer sales, resulting in upward momentum to prices.

Another consideration is the move from small molecule drugs to biotherapies such as monoclonal antibodies. The methods of manufacture for biotherapies are considerably more complex and hence expensive than for conventional therapies, and this is necessarily reflected in their prices. However, Rader and Langar [6] report that the efficiency of the production of biopharmaceuticals improved hugely between 2001 and 2014; the yield

increasing from 1 to 2.56 gram/litre. This suggests that the cost of manufacturing should lower drug prices during this period. It has not. The complexity of manufacture also creates a non-IP (Intellectual Property) barrier to market entry, which means that the end of the patent's life does not automatically equate to generic entry and monopoly prices can continue for longer than the patent period. The complexity of manufacture for biologic products, is accepted to be orders of magnitude more complex than conventional small molecule therapies. There is real concern that apparently identical production processes will not produce equivalent products, and this has led to regulators to create new regulatory pathways for biosimilar products – the equivalent of generics for biologic products – included the requirement of clinical trial evidence to support a claim of therapeutic equivalence. These regulatory requirements mean that much larger upfront investments are required to compete with biologic products after patent expiry. All other things equal, this makes biosimilars a less attractive investment opportunity than generics for small molecule therapies. It also reduces the pool of companies who have the financial and technical resources required to launch a competitor product.

An alternative explanation that has gained increasing credence in the media is that the rising price of drugs reflects what the market will bear, rather than value or costs of R&D. During the early 2000s treatments for rare diseases – referred to as Orphan Drugs – were launched with prices in excess of \$100,000/patient/year^{vi}. Whilst this was protested, it was paid. In the context of a market, the decision to pay these extremely high prices was a signal to drug manufacturers that the willingness to pay for health gains was considerably higher than had previously been assumed. As drug manufacturers are commercial organisations with a legal duty to maximise shareholder value, and hence profits, it was entirely predictable that the prices for new drugs would increase in response to the information implicit in the decision to pay premium prices for orphan drugs.

110 ***Decisions on allocation of resources***

111 Clearly governments have a driving role in allocation of resources. The use of health
 112 technology assessment (HTA) to guide these decisions is well-established in the majority of
 113 developed countries and is becoming increasingly prevalent in developing countries. The
 114 belated realisation by government bodies that manufacturers will seek to maximise the
 115 profit from their therapies has led to a range of novel policy responses with heightened
 116 political significance. The issue of drug prices, including the price of cancer drugs was an
 117 issue in the 2016 US Presidential election^{vii-ix}, and continues to be a key issue for the Trump
 118 Presidency^x. A number of State Governments have developed 'Transparency Bills' that force
 119 drug manufacturers to disclose how much they spent on R&D of new drugs, to inform
 120 judgements about what prices would represent a 'fair return' on that investment [7].

121 Clinicians have also become increasingly publicly concerned about the cost of new cancer
 122 drugs. In 2012 three physicians at the Memorial Sloan-Kettering Cancer Hospital took a
 123 public stand, refusing to prescribe Zaltrap, the vascular endothelial growth factor (VEGF)
 124 inhibitor also known as aflibercept, for their patients because it 'has proved to be no better
 125 than a similar medicine we already have....while its price – at \$11,063' is twice as high"^{xi}.
 126 One of these physicians, Peter Bach, subsequently led the development of the 'Drug
 127 Abacus'^{xii}, which explicitly assesses the value of cancer drugs. The National Comprehensive
 128 Cancer Network incorporated affordability into its 'Evidence Blocks' Clinical Guidelines^{xiii}. In
 129 October 2015 a group of patients and clinicians called on the UK Government to over-ride
 130 Roche's patent on its Breast Cancer drug Kadcyra, because the £90,000, was considered too
 131 high^{xiv}.

In the UK, the individual cost and total budget impact of new cancer drugs became so acute that in 2010 a dedicated Cancer Drug Fund (CDF)^{xv} was established. This allowed consideration of funding for drugs not currently appraised or recommended by the National Institute of Clinical Excellence (NICE). In 2015, having exceeded its allocated budget, its remit changed, with a view to generate evidence for promising but still unproven new cancer therapies whilst ensuring that the total budget impact did not destabilise the UK health system's general pharmaceutical budget. Currently the CDF considers drugs that have been assessed by NICE to have the potential to be cost-effective and approval is based on the premise of further data collection to reduce uncertainty on cost-effectiveness estimates and to further price negotiations between the manufacturer and Department of Health. Whilst it had many problems, with one analysis finding that the CDF had not delivered meaningful value and may have exposed patients to toxic side effects^{xvi} this mechanism was designed to link the price of new cancer drugs to their effectiveness. It also addressed concerns that too rigid an application to value-based market access will eliminate potentially valuable therapies from the health systems formulary before they have had chance to prove their value. The original version of the CDF was designed to be a stop-gap measure, whilst a programme of Value Based Pricing was developed to replace the long established UK Pharmaceutical Price Regulation Scheme (PPRS) (see Text Box 1).

So who should make decisions on how these resources should be allocated and how should they do it? What role and responsibility should the individual physician bear? As clinicians we are used to being our patients' advocate, and lobbying for patients under our care on an individual basis to be able to access drugs through commercial access schemes, compassionate use programmes and clinical trials. The decisions we make with patients

regarding treatment options are also frequently emotionally charged, and the emotional and ethical considerations of treatment choices in relation to expensive personalised drugs need to be considered.

Ethical considerations

Medical students are taught about the four pillars of ethics described by Beauchamp and Childress: autonomy, beneficence, non-maleficence, and justice [8]. The right of a patient to choose or refuse their treatment, or autonomy, could be interpreted as all patients having the right to access personalised SACT if appropriate and indicated. Simply put, if they want a treatment that has evidence of efficacy they should be able to have it. Realistically this is limited by local access and funding. Beneficence dictates we should act in the patient's best interests. In the context of resource allocation this can be difficult to bring into accordance with non-maleficence, or *primum non nocere*: first, do no harm. We have to consider to whom we have a duty of care: individual patients, all patients under our care, all patients nationwide or even globally. If we act in a single patient's best interest and allocate resources to an individual, other patients whose care is funded by the same budget may not be able to access treatment and therefore have been harmed. By following the principle of beneficence for one patient we may inadvertently go against the principle of non-maleficence for another, or potentially many. The opportunity cost needs to be considered.

The fourth principle of justice balances some of these concerns, with the premise of ensuring fair and equal treatment for all. To consider the treatment of other hypothetical patients as a clinician when one patient is in the clinic room in front of you is difficult. Perhaps one mentality physicians adopt is to advocate their individual patient's treatment

with the assumption that other patients will be equally advocated by their physicians, and that it will all 'balance out'. However there is significant geographical variation in access to SACT through the CDF in the UK^{xiii}, and on a global scale we know that access to personalised medicine is extremely limited in low and middle income countries and this further worsens the health divide between these economies [9].

The question of how to ethically allocate a personalised SACT drug is relevant at a patient's first consultation with a physician, deciding local funding policy; orchestrating governmental policy; development of national and international guidelines; and the influence of the pharmaceutical industry and media. It is unrealistic and unfair to expect clinicians or economists at the present time to be able to precisely predict all the consequences of proposed treatments or policies at population level, given the complex nature and influence of these events. In the future methodological systems may exist to facilitate this to allow clinicians more control over balancing ethical and financial decisions. Generally clinicians will follow local or national guidelines which include drugs that can be funded locally, and therefore it is vital that these are made with cost-effectiveness, efficiency and ethics in mind.

In addition to the ethical issues regarding allocation of treatments there are also ethical issues regarding the diagnostic side of personalised oncology. Patients may, through routine practice, clinical trials or self-funded through direct to consumer (DTC) genetic testing, be tested for genetic or biological markers which do not link directly to treatment decisions or options. Patients may develop inaccurate expectations of treatment based on these tests or be psychologically distressed if they feel they have an aspect of their diagnosis they are

199 powerless to ‘treat’, the issues raised around these tests can also have profound effects on
200 family relationships¹⁰.

201 Having access to international guidelines which do not take financial constraints into
202 account such as American Society of Clinical Oncology (ASCO) or European Society of
203 Medical Oncology (ESMO) guidelines can give conflicting recommendations. Knowledge that
204 there may be a superior treatment plan than one a patient can access locally provides
205 physicians with an ethical dilemma, between complying with local guidelines which have
206 included cost-effectiveness in their work up and may better comply with the principle of
207 justice, and advocating treatment for the individual patient based on international
208 guidelines which would represent the principle of beneficence. Value frameworks provided
209 by ASCO and ESMO exist which attempt to take cost into account with potential benefit to
210 quality of life, these may be helpful on an individual level but are less helpful for population-
211 level reimbursement decisions; their scoring systems also reflect implicit values about the
212 relative importance of different domains which may not represent the individual’s priorities.
213 Another complicating factor is that physicians are frequently involved in managing
214 healthcare resources or writing regional, national or international guidelines.

215 To be just, these guidelines need to be developed transparently with input from patients,
216 clinicians, and the funding/provider parties. An example of this is NICE^{xviii} in the UK, which
217 includes engagement with all relevant parties at every stage of the appraisal process for
218 specific new strategies, and a formal citizens’ council which reviews the underlying moral
219 and ethical principles behind reimbursement decisions.

The concept of acknowledging ethical considerations in HTA is not new and has been discussed since the conception of HTAs in the 1970s. However ethical issues have been shown to only be included in a minority of HTAs in numerous studies¹¹⁻¹³. Hofmann in his review of the issue discusses reasons why ethics is so seldom included in HTA¹⁴. These include: poor inclusion of ethicists in HTA, no common agreed methodology for integrating ethics, ethics methodology appears to be deficient, insufficient, or unsuitable, integrating ethics in HTA is neither efficient nor needed for successful HTA, most moral issues are general and not specific to a given technology, all relevant ethical issues can be handled within other frameworks such as economics, and that ethics can undermine or burst the foundation of HTA¹⁴. The debate on if and how ethics could be formally included into HTA is complex; one viewpoint is that as healthcare itself is integrally ethical, ethics cannot be removed from its allocation, the only question is how to formalise this. Merging the practical, the moral and the philosophical is a difficult task.

From a clinician's personal viewpoint, as long as these local guidelines are developed by ethically accountable processes robust to judicial review, clinicians on an individual basis may be satisfied the interests of their patients are fairly advocated [15]. It could be argued that to be truly just and demonstrate accountability for reasonableness, patients who bear the opportunity cost should also be represented [16,17].

Concluding Remarks

It is likely that the reimbursement environment for cancer drugs will become more challenging in the future. The push back from patients, clinicians, payers and governments

has begun. There are implications of the changing reimbursement environment for developers of future cancer therapies, including precision medicine. Achieving regulatory approval in major markets, principally the US and the European Union, has historically been the purpose of clinical translational research. The focus has therefore been on meeting the relevant regulatory requirements, for safety and efficacy. This has shaped the design of research and development (R&D) processes, disproportionately to the likely value of the new drug.

This is likely to be increasingly common unless developers change how they think about developing their R&D processes. Approximately 90% of drugs entering phase 1 clinical trials fail, in oncology the probability of drugs in phase I trials to gain FDA approval has been calculated at 6.7% [18]. The addition of failure at the reimbursement phase of translation may make the development of further precision medicine drugs too risky for developers to invest. We need to rethink how we develop and test these drugs. Companies that have invested millions in drug development understandably need to see a return on their output or they will go out of business. But how much profit is 'enough'? The focus on investment into R&D cannot only be on being reimbursed. The needs of the payers, as well as those of the licencing authorities and regulators need to be considered (Text Box 2). A measured and balanced approach to R&D development decisions is needed to weigh these multiple factors.

Bubela and McCabe have proposed a structured framework evaluating candidate technologies from a value perspective, discussed further in the Outstanding Questions section [19]. Priority should be given to technologies for which there is substantial headroom for improvement in health. By avoiding developing technologies for which there

265 is neither substantial nor valued need, the limited financial resources available for
266 translating precision medicine technologies, can be allocated more appropriately and have a
267 greater impact on future cancer therapies.

268 There is no easy solution to these dilemmas. See Outstanding Questions for a list of the
269 main issues still to tackle. Health economics and its direct relevance to patient care must be
270 included in medical education from an undergraduate level, and continued in postgraduate
271 training. For clinicians to feel they have understanding of these issues this must be a subject
272 discussed at medical conferences with representation by economists and discussion
273 between clinicians, economists and those involved in developing guidelines and allocating
274 resources.

275 For guidelines to be developed ethically regarding the allocation of these resources the
276 concept of accountability for reasonableness is useful, advising that guideline development
277 and assessment for funding is undertaken by a group which includes patients who bear the
278 opportunity cost. The process needs to be fully transparent with a process for appeal. The
279 use of technology widely available such as videoconferencing and/or streaming these
280 discussions live may facilitate this.

281 A structured framework which evaluates candidate technologies from a value perspective
282 can help avoid developing technologies for which there is neither substantial nor valued
283 need. Priority should be given to technologies for which there is substantial headroom for
284 improvement in health – i.e. conditions where the health lost by each affected individual,
285 compared to a full quality adjusted life expectancy, is substantial. Also, conditions
286 associated with expensive costs to health care systems offer an opportunity for technologies

that achieve the same or better outcomes at a lower price. In assessing the headroom for a new technology it is important to examine forecasts of which technologies might be on the market at future time points. Careful analysis of clinical trial and patent databases can be used to identify technologies that are ahead in the translational pipeline. This can provide insight into the true headroom for a technology at the start of the translational process.

In these complex issues which involve global and local economics, politics, and the media we must retain focus on the core issue – *how can we get the right drugs to the right patients?* With a joint development of these frameworks we may be able to get a cohesive solution to an expensive problem. In addition to politicians, pharmaceutical industry investors, economists and journalists, physicians have to represent their interests – the patient – in these discussions. How else will we be able to look our patients in the eye and say, “I have the right drug for you”?

Value Based Pricing

The fundamental idea behind Value Based Pricing is that the price paid for a new drug (or indeed any health care intervention) should reflect the value that it produces. If a health care payer can be explicit about what is valued and how much it is willing to pay for a given amount of that value, then for any given technology, an assessment of the value produced

will lead directly to the price that will be paid. For example, consider a new drug that produces an additional two years of good health compared to current treatment. If we measure years in good health as QALYs and the health care payer is willing to pay up to £30,000 per QALY, then the *maximum* price for the new drug would be $2 \times £30,000 = £60,000$ [27]. In reality Value Based Pricing is much more complicated as the value of health gain tends to be affected by other factors such as the age/stage of life of the recipient, the severity of the health problem and even the characteristics of the technology itself [28]. When the UK government attempted to develop a Value Based Pricing framework, based upon consultations with the UK population, they were unable to identify a framework that was acceptable to all stakeholders in the negotiations [29]. As a result, the plans were scrapped and new 5 year PPRS agreement was implemented in its stead.

Value Based Pricing is only one of many alternative market access proposals that have been proposed by both policy makers and academics over the last two decades. Whilst these schemes have many different names, they can be considered in three categories: Pay for Performance (P4P) which link the price that a manufacturer receives to the observed value of technology in practice, Only with Research (OWR) which make the therapy available for all patients with an agreed clinical indication(s), as long as a pre-defined research study is underway (although the patient in question does not need to be enrolled) and Only in Research (OIR) which makes a therapy available for patients enrolled in a pre-defined research study that is designed to address a weakness in the existing evidence base.

363

Regulator vs payer approach to evidence

Regulators' and payers' approach to evidence differ in two important ways. The first is that payers are interested in effectiveness rather than efficacy; i.e. how well does a technology work in the real world rather than how well does it work in ideal circumstances. The second is that payers are interested in actual health benefits when they consider effectiveness, rather than biological surrogates of health such as tumour shrinkage or progression free survival. The use of surrogates by regulators is one of the major sources of uncertainty in the evidence base for effectiveness and value. For payers, uncertainty has a cost, which can be measured. The value of the health gain is frequently characterised as the payer's willingness to pay for health. If the expected value of making the wrong decision is sufficiently large, payers may choose to require more research either as part of the implementation of the technology into the health system (OWR), or withhold reimbursement until more research is undertaken (OIR). If the payers require further research, the time for all patients who could benefit from the therapy to access it may be extended.

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